Measuring the effects of HPV16/18 vaccination on HPV positivity and anogenital warts

Valorization

Of all infectious diseases, human papillomavirus (HPV) infections are associated with the highest disease burden in the Netherlands. Sexually transmitted HPV can cause anogenital warts, recurrent respiratory papillomatosis, and various anogenital and head-and-neck cancers in both men and women. Cancers with an established HPV etiology include cervical, vaginal, vulvar, anal, and oropharyngeal cancer in women; and penile, anal, and oropharyngeal cancer in men. The estimated yearly number of cancer diagnoses attributed to HPV in the Netherlands was over twelve hundred in the period 2008-2017 and almost fifteen hundred in 2019. The estimated yearly number of anogenital warts diagnoses was over forty-three thousand in the period 2017-2018. Sexually transmitted HPV infections are very prevalent in the general population and the vast majority of the sexually active people will acquire an HPV infection at least once during lifetime. Infections are not restricted to specific groups at high risk of infection, making the prevention of HPV infections of public health importance. Prophylactic vaccination is viewed to be best possible prevention strategy and historically vaccination programs have achieved major public health benefits.

Prophylactic HPV vaccination was introduced in the Netherlands in 2009 for young girls using the bivalent HPV vaccine that targets the most oncogenic types HPV16 and HPV18. Each year all 12-year-old girls are invited for HPV vaccination. From 2021 onwards, even the entire cohort of boys and girls will be invited for HPV vaccination annually. This highlights that the effects of HPV vaccination are of societal relevance. In this thesis, we assessed the individual- as well as the population-level effects of HPV vaccination on HPV positivity and anogenital warts.

At the time of HPV vaccine introduction in the Netherlands in 2009, there were some uncertainties regarding the effectiveness of HPV vaccination, for example about the direct vaccine effectiveness in a “real-life” setting among the target population of (pre)adolescents, the duration of protection, the level of cross-protection, or the possible occurrence of type-replacement. This thesis has given insight into many of these questions. Lessons learned from this thesis, that are relevant for public health, include:

- The vaccine effectiveness of bivalent HPV vaccination is high against the most oncogenic vaccine-targeted HPV types 16 and 18;
- There is relevant cross-protection against non-vaccine oncogenic HPV types;
- The vaccine effectiveness is high at least up to 7/8 years after vaccination, with no signs of reduced effectiveness over time;
- The vaccine effectiveness against anal HPV positivity is comparably high as against genital HPV positivity;

- The HPV vaccination program has reduced the transmission of HPV in the population, leading to less infections among those unvaccinated, with the exception of men who have sex with men;
- There are no indications for type-replacement up to 8 years after the introduction of the HPV vaccination program;
- The bivalent HPV vaccine might provide partial protection against anogenital warts.

The lessons learned in this thesis have already contributed to the intended changes in the HPV vaccination policy. The Dutch Health Council valued our research in recommending about the new HPV vaccination program. For example, the sustained high VE, was taken into consideration in the recommendation to lower the age at which vaccination should be offered from 12 to 9 years of age. Moreover, our finding that herd effects are measurable within 6 to 8 years after HPV vaccine introduction, was an important observation for the Health Council to recommend extension of the vaccination program to boys. They viewed our observed herd effects as evidence that adding boys to the program will not only result in the individual prevention of boys themselves, but will also add to the protection of unvaccinated women through herd protection.

The results of this thesis are also relevant for the choice of vaccine to be used in the HPV vaccination program, as demonstrated by the acknowledgement of our results in the tendering procedure of 2020 to contract an HPV vaccine for the restructured vaccination program starting in 2021. Up to date, there are 3 prophylactic vaccines that target HPV; a bivalent vaccine that targets the most oncogenic HPV types 16 and 18; a quadrivalent vaccine that targets HPV types 6 and 11 (that cause the majority of the anogenital warts) in addition to HPV types 16 and 18; a nonavalent vaccine that targets the oncogenic HPV types 31, 33, 45, 52, and 58 in addition to HPV types 16, 18, 6, and 11. The 3 vaccines are all licensed for men and women and indicated to prevent genital (cervical, vulvar, and vaginal) and anal (pre)cancers caused by the HPV vaccine types. The quadrivalent and nonavalent HPV vaccines are also indicated to prevent anogenital warts. The cross-protection of the bivalent vaccine against non-vaccine oncogenic HPV types as found in our studies is higher than that generally observed for the quadrivalent vaccine, making the bivalent vaccine superior in terms of cancer prevention. The cross-protection of the bivalent vaccine also diminishes the difference in cancer prevention between the bivalent and the nonavalent vaccine. The differences between the bivalent and nonavalent vaccine are even further diminished with the apparent partial protection of the bivalent HPV vaccine against anogenital warts. Taken together, the results of this thesis underscore the necessity to conduct proper cost-effectiveness analyses to compare the different HPV vaccines, taking into account cross-protection against the different HPV types and possible protection

against anogenital warts. Because the HPV vaccination program is publicly funded, it is important to have good value for money.

By studying the individual- and population-level effects of HPV vaccination, we demonstrated the benefits of HPV vaccination. We estimated a vaccine effectiveness of 90% against the most oncogenic HPV types HPV16/18 and a reduction of 13% each year in the HPV16/18 prevalence among women and heterosexual men. With the observed cross-protection and protection against anal HPV, the benefits of bivalent HPV vaccination even go beyond initial indications of the registration of the vaccine. These results are useful to create public awareness about HPV infections and the importance of HPV vaccination, for example via media attention. These results are also useful to inform the general public and health care providers. Previous studies indicated that health care providers play an important role in the decision-making process to vaccinate. Informing both the general public and health care providers about the effectiveness of HPV vaccination, could possibly increase the HPV vaccination coverage. Currently, there is a lot of misinformation about HPV vaccination, mainly concerning side effects. Moreover, there are misperceptions about the effectiveness of HPV vaccination. The bivalent HPV vaccine that is used in the Netherlands might be conceived to protect only against the 2 HPV vaccine types, while broad cross-protection against multiple HPV types has been clearly demonstrated in our studies as well as in others. Another misperception is that HPV vaccination is believed to be ineffective once someone has had sexual intercourse. Our results show it is not necessarily too late to vaccinate after sexual debut. Even in a highly sexually active population of visitors of sexual health centers, many individuals seem to be still unexposed to the HPV vaccine types, indicating the vaccine effectiveness could be high.

The results of this thesis give rise to targeted HPV vaccination of men who have sex with men (MSM) visiting sexual health centers, as we showed that MSM have not yet benefitted from the girls-only vaccination program to a large extent and many MSM seem to be susceptible to HPV when visiting the sexual health center. An HPV vaccination program targeting MSM has the potential to have a major impact on the HPV prevalence among MSM who are at high risk for anal and oropharyngeal cancer; with the current girls-only HPV vaccination program about 566 life years are lost due to vaccine-preventable HPV-related cancer among MSM each year. However, the HPV vaccine effectiveness in the target population of MSM visiting sexual health centers is unknown. This thesis has contributed to an innovative ZonMw research proposal to assess the vaccine effectiveness among MSM aged ≤26 years who visit the sexual health center of Amsterdam, HPV-ECSTASE (Human Papillomavirus Vaccine EffeCtiveness STudy Among men who have SEx with men). Results of this study can inform policy on the desirability to roll out a targeted vaccination program nationally.

Next to the lessons learned about the vaccine effectiveness among women and the population-level impact of the current girls-only HPV vaccination program, we also provided a framework to monitor the effects of the upcoming changes in the HPV vaccination program. Because in the PASSYON study the HPV prevalence is measured among both men and women, the PASSYON study can be used the measure the vaccine effectiveness among men after sex-neutral vaccination is implemented. Moreover, in the PASSYON study there is information available of the HPV prevalence from pre- girls-only vaccination and pre- sex-neutral vaccination, enabling to study the additional population-level impact after switching to a sex-neutral vaccination program. With the unique design of the PASSYON study, different effects of the upcoming changes in the HPV vaccination program can be studied. In close collaboration with policy makers and observations from other studies, this research can direct the future of the HPV vaccination program in the Netherlands.